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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/[illegible],020	05/06/97	MARCINIAK	I

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EXAMINER	
FRIEBE,J	

ART UNIT	PAPER NUMBER
1819	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

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Office Action Summary	Application No. 08/852,020	Applicant(s) Maruyama et al.
	Examiner Scott D. Priebe, Ph.D.	Group Art Unit 1819

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-29 is/are pending in the application.

Of the above, claim(s) 21 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-20 and 22-29 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Serial Number: 08/852,020

Art Unit: 1819

DETAILED ACTION

The claims of this application contain underlining or brackets that are intended to appear in the printed patent or are properly part of the claimed material. Under these conditions, proposed amendments to the claims may not be made by underlining words added or by bracketing words to be deleted. See 37 CFR 1.121(d).

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claim 1-20 and 22-29, drawn to recombinant lambdoid bacteriophage vectors, recombinant lambdoid bacteriophage particles, and methods of using and making recombinant lambdoid bacteriophage particles, classified in Class 435, subclasses 5, 6 and 320.1.

II. Claim 21, drawn to a fusion protein, classified in Class 530, subclass 350.

The inventions are distinct and/or independent, each from the other because of the following reasons:

The recombinant lambdoid bacteriophage vectors of Group I and the fusion protein of group II are independent and patentably distinct compounds which have different chemical compositions, structures, and functions. The use of each does not require the use of the other.

The fusion protein of Group II and the method of using the recombinant bacteriophage of Group I are indirectly related as product and process of use. The inventions can be shown to be

distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the fusion protein can be used independently of the bacteriophage as a diagnostic reagent and can also be used to generate antibodies against the preselected polypeptide moiety.

The method of making the recombinant bacteriophage of Group I and the fusion protein of Group II are indirectly related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (M.P.E.P. § 806.05(f)). In the instant case the fusion polypeptide could be made by solid phase synthesis or by recombinant expressing from a plasmid vector without producing recombinant phage particles.

The recombinant lambdoid bacteriophage particles of Group I and the fusion protein of Group II are related as combination and subcombination. Inventions in this relationship are distinct if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability, and (2) that the subcombination has utility by itself or in other combinations. (M.P.E.P. § 806.05(c)). In the instant case, the combination as claimed does not require the particulars of the subcombination as claimed because as disclosed in the specification the recombinant bacteriophage can be used to infect host cells for transfer and propagation of the vector, such infection does not require the presence of the fusion polypeptide.

The subcombination has separate utility such as for the production of antibodies against the preselected polypeptide moiety, also as disclosed in the specification at page 98, lines 3-5, the fusion protein can be used as a diagnostic reagent.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and the search required for Group I is not required for Group II, restriction for examination purposes as indicated is proper.

During a telephone conversation with Emily Holmes on 12/8/97 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-20 and 22-29. Affirmation of this election must be made by applicant in responding to this Office action. Claim 21 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(h).

Drawings

This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Claim Objections

Claims 8 and 11 are objected to because of the following informalities: In claim 8, line 2, "has a amino" should be "has an amino". In claim 11, line 4, a comma should be inserted between "protein" and "surface". Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 10 and 28-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The application contains bacteriophage strain lambda foo and *E. coli* strains EQ166, CA168, and MC8 that are encompassed by the definitions for **biological material** set forth in 37 C.F.R. § 1.801. Because it is apparent that these bacteriophage and bacterial strains are essential for practicing the invention of claims 10, 28-29, they must be obtainable by a reproducible method set forth in the specification or otherwise be known and readily available to the public as detailed in 37 C.F.R. §§ 1.801 through 1.809. The applicants' assertion that bacteriophage strain lambda foo and *E. coli* strain MC8 were deposited is noted. However, all of the requirements of C.F.R. §§ 1.801 through 1.809 have not been met. In particular, applicants failed to comply with 37 C.F.R. § 1.809(d).

The following is a quotation of 37 C.F.R. § 1.809(d):

" For each deposit made pursuant to these regulations, the specification shall contain: (1) The accession number for the deposit; (2) The date of the deposit; (3) A description of the deposited biological material sufficient to specifically identify it and to permit examination; and (4) The name and address of the depository."

Specifically, the specification lacks the ATCC number for each at page 133 of the specification. Submission of the deposit contract would avoid the issue of potential new matter.

Furthermore, there is no indication that *E. coli* strains EQ166 and CA168 have been deposited. While these strains may currently be available, there is no guarantee that they would remain so for the effective life of the patent. It would not be possible to reconstruct these strains based solely on the relevant genotype given for each in the specification. Since these strains are specifically recited in the claims, they are deemed to be essential for practicing the invention as claimed.

If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strains have been deposited under the Budapest Treaty and that the strains will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

Claims 1-3, 6-8, 11-12, 15-20, and 22-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited to vectors encoding or bacteriophage particles comprising fusions with lambdoid bacteriophage tail polypeptides that

are pV, does not reasonably provide enablement for embodiments wherein the lambdoid phage tail proteins are other than pV . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. .

The claims are drawn to or recite bacteriophage vectors or particles comprising DNA or proteins that encode or include a tail polypeptide as part of a fusion protein for the purpose of displaying preselected polypeptide on the surface of the phage tail. As admitted in the specification at page 20, only the products of genes J, V, G, M, and T are assembled on the surface of the tail and therefore suitable for displaying the preselected polypeptides, the remaining tail proteins are presumably unsuitable. The specification provides specific guidance and working examples only for the major tail protein pV and the prior art is silent on fusion proteins that include the tail proteins. Reference to the other tail proteins is merely suggestive that they are suitable for use in the invention by virtue of their location on the surface of the phage tail. Thus, the breadth of the claims is not commensurate in scope with the disclosure in the specification.

The specification discloses that the pV is present in 180 to 200 copies in the mature tail. At page 115, 1st paragraph of the specification, it is taught that addition of a linker polypeptide appears to interfere with tail assembly, since the plaques were smaller in su^+ hosts. Further, at page 126 of the specification it is disclosed that phage tails displaying beta-galactosidase contained only one to a few copies of the fusion polypeptide even though higher levels of incorporation could have been expected, indicating that the fusion polypeptide interfered with

some aspect of tail assembly. These findings illustrate that even though the carboxy terminus of pV is dispensable, fusion to a foreign polypeptide interferes with some aspect of tail assembly or infection. Therefore, successful incorporation into a mature tail of pV protein fusions is somewhat unpredictable.

Each of the tail proteins occupies a unique position in the mature tail, and performs a unique role during tail assembly (see Katsura, page 336). The successful incorporation into the tail of altered forms of one of the tail proteins, e.g. pV, does not provide evidence that any of the other tail proteins can be similarly modified without impairing their unique role in tail assembly. With respect to the pV protein, it was known in the prior art that this protein comprised a "knob" that extended out from the surface of the phage that was dispensable. It is this "knob" that is replaced by the displayed peptide in the disclosed invention. Replacement of this knob with heterologous peptide sequence would not have been expected *a priori* to interfere with phage assembly, however, as disclosed in the instant specification it was necessary to replace the knob with the desired peptide in only a limited number of recombinant pV subunits in the phage tail, or assembly was impaired. It is for this reason that Ladner is not deemed to be prior art for the prophetic disclosure of using pV peptide fusions to display proteins. No comparable dispensable peptide sequence is disclosed in either the specification or the prior art that one could have expected could be replaced with a desired peptide, without interfering with phage assembly. As recited in the claims, the fusion polypeptide consists of, from amino to carboxy terminus, a tail polypeptide, a linker polypeptide and a preselected polypeptide. Such an arrangement would

therefore require that the carboxy terminus of a given tail polypeptide be exposed on the surface of the tail and that addition of other polypeptides to the carboxy terminus of the tail polypeptide not interfere with either tail gene expression, tail assembly, or infection. In the case of the latter, infection would be necessary to propagate the phage for isolation and further manipulation, i.e. the use of the invention. Neither the specification nor the prior art disclose information that would suggest to the skilled artisan that fusion proteins comprising pJ, pG, pM, or pT at the amino terminus and a foreign polypeptide at the carboxy terminus could successfully be assembled into a phage tail or, if it could be incorporated, whether the resulting phage particles would be capable of infecting a host. With respect to pJ, the tail fiber protein which interacts directly with a host membrane porin for successful infection, clearly a phage having a fusion pJ protein would be unlikely to retain it's ability to bind host cells. In the absence of such information, there is no predictability on the success of displaying polypeptides as fusions to tail proteins other than pV. As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

The instant specification does not provide sufficient information to allow one skilled in the art to predict *a priori* whether or not the tail proteins of the phage genes other than gV, e.g. J, G, M, and T, could accommodate a heterologous peptide, and if so where, such that the recombinant phage tail protein could be assembled into the phage tail. Therefore, one skilled in the art could not make and/or use the vectors and bacteriophage particles comprising tail protein fusions other than those involving pV without undue experimentation.

Claims 5 and 14 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to pV which includes residues 1-176 of SEQ ID NO 6 or SEQ ID NO 1, in the case of claims 5 and 14, respectively . See M.P.E.P. §§ 706.03(n) and 706.03(z).

The claims are limited to pV fusion proteins or vector sequences encoding them which include amino acid residues 1-176 of SEQ ID NOs 1 or 6 and "conservative substitutions thereof". The specification does not disclose or teach what would constitute "conservative substitutions thereof", it is assumed that the phrase refers to conservative amino acid substitutions. The specification discloses only one example of amino acids 1-176 of pV that can be used successfully in the claimed inventions. Thus the breadth of the claims is not commensurate in scope with the enabling disclosure. It is known in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable (see Ngo, pp. 433

and 492-495). The specification contains no guidance or citations of relevant prior art that would inform the skilled artisan of which amino acid residues of pV could be altered without adversely affecting its folding or its ability to assemble into the phage tail. In the absence of such guidance, one skilled in the art would not be able to practice the invention as claimed without undue experimentation.

Claims 5, 7, 9-20, 22-26, and 29 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claims 5 and 14 are indefinite for recitation of "and conservative substitutions thereof". As the claim is written it is not clear whether the phrase refers to conservative substitutions of pV or of amino acid residues.

Claim 7 is indefinite for recitation of "from about 10 to about 100". The phrase fails to set forth the metes and bounds of the claim since it is not clear whether lengths of less than 10 or more than 100 are included.

Claim 9 is indefinite for recitation of "has a nucleotide sequence shown in SEQ ID NO 5". As written it is not clear whether the phrase refers to the entire sequence of SEQ ID NO 5 or some portion of the sequence. If the former is intended, it is suggested that the claim be amended to recite --has a nucleotide sequence from 1 to 910 as shown in SEQ ID NO 5--.

Claim 10 is indefinite for recitation of "functionally similar to". It is not clear in what capacity the claimed vector is to be "functionally similar" and in what way the vectors can be dissimilar and yet remain functionally similar.

Claims 11-20 are indefinite for recitation of "consisting essentially of" in claim 11. The basic definition of "consisting essentially of" was set forth in *Ex parte* Davis and Tuukkanen 80 USPQ 448 (Patent Office Board of Appeals) 1949 and applies to compositions not compounds, such as DNA or proteins. The phrase is therefore vague and indefinite in this context.

Claim 13 is indefinite for recitation of "The lambdoid bacteriophage vector", which lacks antecedent basis in claim 11.

Claim 16 is indefinite for recitation of "capable of forming". Does the heterologous protein form a multimeric complex with the fusion protein of not? It is suggested that the phrase be substituted with --which forms--.

Claim 17 is unclear. As part of the tail of the bacteriophage, the fusion protein is part of a multimeric protein. In light of the specification, it appears that the intended multimeric protein is comprised of monomer subunits that are not covalently attached to the tail. Amendment of the claims to more clearly define the multimeric protein would obviate this rejection.

Claims 22-23 are unclear. In order for a library to be formed, the phage particles must contain different species of vector, as recited in claim 23. Claim 22 recites that the particle contains vector of claim 1. However, claim 1 does not recite that DNA encoding a preselected polypeptide is inserted in the vector. The claim only recites that the vector includes a sequence for

insertion of a preselected polypeptide and that the preselected polypeptide would be part of the fusion protein upon suppression. For example, lambda foo is a vector according to claim 1, and a collection of bacteriophage particles each containing lambda foo would not be considered a library.

Claims 24 is indefinite for being dependent on a non-elected claim. It is suggested that the claim be amended to recite the limitations of claim 21.

Claims 25-26 are indefinite for recitation of "able to bind" in step a) of claim 25. Does the ligand or receptor bind the preselected target or not? It is suggested that the phrase be replaced with "which binds".

Claim 29 is indefinite as no ATCC accession number is recited in the claim.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 4, 5, 13 and 14 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1, 3, 9 and 10 of prior U.S. Patent No. 5,627,024. This is a double patenting rejection.

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 6-12 14-20 and 22-29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 5,627,024. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims embrace the claimed invention of the '024 patent.

Priority

The instant application was filed as a division of application number 08/286,888. However, applicant has indicated that the application is to be treated as a continuation under 37

CFR 1.60. Applicant is reminded to amend or replace the declaration and to amend the first sentence of the sepecification accordingly.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

No claims are allowed.

Certain papers related to this application may be submitted to Art Unit 1819 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 9 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, Ph.D., can be reached on (703) 308-2035.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SDP

Scott D. Priebe, Ph.D.
Examiner

December 10, 1997

Jasemine C. Chambers

JASEMINE C. CHAMBERS, PHD.
SUPERVISORY PATENT EXAMINER
GROUP 1800